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Photo-induced formation of cyclopropanols from α-ketoamides via γ-C—H bond activation

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ABSTRACT

A novel type of photocyclization of α-ketoamides was developed, affording unique cyclopropanols bearing amide functionality. *N*-*tert*-Butyl, *N*-trityl, or *N*-non-substituted α-ketoamides with a bulky substituent at the β-position of the amide functionality were efficiently converted to corresponding cyclopropanols through the activation of the γ-C—H bond followed by C—C bond formation between the α- and γ-positions of the amide. Hydrogen abstraction from the γ-position of the amide was considered to be the rate-determining step of cyclopropanol formation, based on the kinetic isotope effect. Cyclopropanols could be converted to two different types of functionalized α-ketoamides depending on the method of ring-opening.

The photochemistry of α-dicarbonyls has been extensively investigated.[1] In particular, the photoreaction of α-ketoamides **1** to produce β-lactam derivatives **2** and/or oxazolidinone derivatives **3** as the main products (so-called Norrish type-II reaction) is well-known (Scheme 1-1)[2] in organic synthesis, because it enables direct C—C (Norrish–Yang cyclization to form **2**) or C—O bond formation (to form **3**) through selective cleavage of the C—H bond[3] at the α-position of the N-atom (Nα-proton). Moreover, the α-dicarbonyl system is conveniently activated by irradiation at relatively long wavelength compared to other standard functional groups in organic molecules. Various applications to the synthesis of biologically active molecules[4] or asymmetric reactions in chiral crystals[5] have also been reported.[6]

Based on the intensive experiments by Aoyama's group[7] and Whitten's group,[8] the mechanism of formation of **2** and **3** was proposed to be as follows (Scheme 1-1). Irradiation of **1** induces n–π^* transition and generates the singlet excited state. The amide functionality serves to quench the excitation state via an electron transfer process to generate the transient zwitterion species **4**. Since the acidity of the Nα-proton would be increased, abstraction of the H-atom followed by protonation of the carbonyl O-atom affords 1,4-biradical species **5** after electron reorganization. According to Whitten's report, β-lactam derivatives **2** are constructed via the intramolecular radical coupling reaction. In contrast, electron transfer can occur again to form another zwitterion species **6** as a precursor of the oxazolidinone derivatives **3**.

In many cases, *N*,*N*-disubstituted α-ketoamides **1** are expected to afford better results as substrates, since the keto-functionality and α-position of the N-atom are placed close to each other. Several examples of photolysis of *N*-monosubstituted α-ketoamides have been reported.[9] On the other hand, photo-induced cyclopropanol formation of ketones[10] has been reported only for a limited range of substrates, such as β-amino-,[11] β-oxy-,[13] or α-methylene-ketones,[12] in which the 1,4-hydrogen shift would be facilitated due to stabilization of the radical at the β-position by a heteroatom or double bond. However, as far as we know, no example of photo-induced cyclopropanol formation of α-ketoamides has been reported. We hypothesized that the formation of cyclopropanol **8** would be possible for *N*-monosubstituted α-ketoamides **7**, which favor *s*-trans conformation (Scheme 1-2). In contrast to the simple ketone, α-ketoamides **7** are expected to be activated by irradiation at a longer wavelength (longer than 300 nm) and to generate the transient zwitterion species **9**. We speculated that the amide functionality in **9** would facilitate abstraction of the unactivated γ-C—H bond to generate

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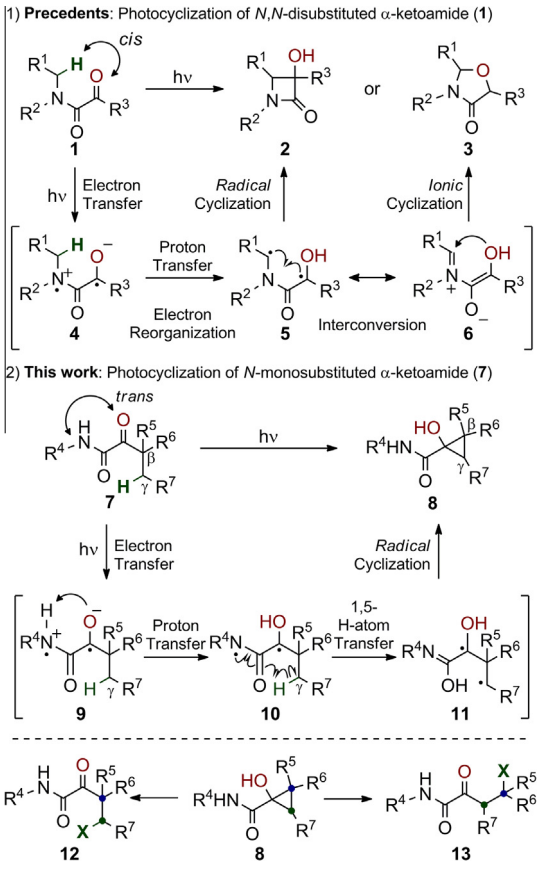
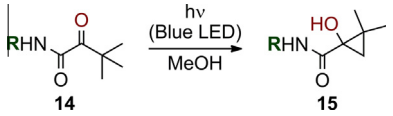


Scheme 1. (1) Photo-reaction of α-ketoamides; (2) working hypothesis for the formation of cyclopropanol derivatives.

1,3-biradical species **11**, which is then converted to the cyclopropanol product. Namely, the rapid proton transfer from the N-atom to the oxygen atom (from **9** to **10**, instead of transfer of the Nα-proton in the case of **1**) and the 1,5-hydrogen shift from the γ-position to the amide owing to its radical character (from **10** to **11**) result in γ-C—H bond activation.[14] The highly substituted cyclopropanol **8** bearing amide functionality is expected to be a unique synthetic building block for organic synthesis. Since various types of ring-opening reactions of cyclopropanol[15] are known, **8** could be converted to the γ-position-functionalized amides **12** or **13**. The overall transformation is regarded as functionalization of the γ-position, with or without rearrangement of the framework.

To test our working hypothesis, 3,3-dimethyl-2-oxobutyramides **14** having a substituent on the N-atom were selected as substrates for initial examination. Normally, functionalization of the C—H bond on the *t*-butyl group is challenging without a special directing group,[16] but we expected that 3 equivalent methyl groups at the γ-position would facilitate the desired reaction (Table 1). All reactions were conducted in glass tubes under a blue LED lamp (max. output 365 nm) under degassed conditions (see Fig. S1).[17] Preparation of α-ketoamides **14** is summarized in Schemes S1 and S2.[17] As we expected, photolysis of benzyl amide **14a** gave the isolable cyclopropanol **15a**, though in low yields (entry 1). Neither β-lactam **2** nor oxazolidinone **3** was detected. Instead, imide **14b** or its cyclized product **15b** was isolated. This observation suggested that H-atom abstraction from the Nα-proton competes with the desired reaction pathway. Hence, imide-type **14b** (phenyl) and **14c** (*n*-pentyl) without Nα-protons were investigated as substrates. As a result, cyclopropanol formation was slightly improved, but degradation of the substrates

Table 1
Effect of substituent on N-atom



14 15

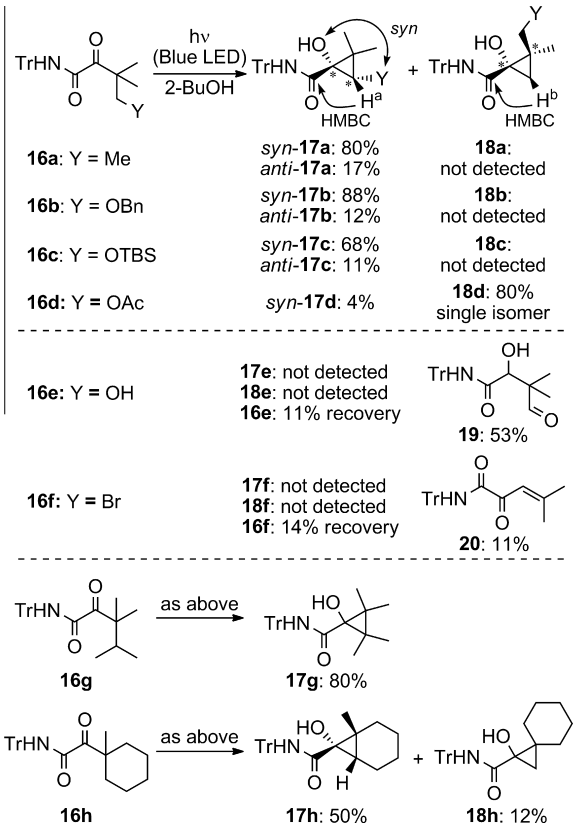
Entry	Substrate	R	Time (h)	Product: yield (%)
1	**14a**	CH_2Ph	1.5	**15a**: 13[a]
2	**14b**	COPh	11	**15b**: 28
3	**14c**	$CO(CH_2)_4CH_3$	1	**15c**: 31
4	**14d**	O^{t}Bu	12	**15d**: 0[b]
5	**14e**	^{t}Bu	3	**15e**: 71
6	**14f**	CPh_3	12	**15f**: 50[c]
7[d]	**14f**	CPh_3	11	**15f**: 99
8	**14g**	H	5 min	**15g**: 94

[a] **14b** (31%) and **15b** (24%) were obtained.
[b] Starting material was recovered (98%).
[c] Starting material was recovered (49%).
[d] Reaction solvent: 2-BuOH.

was still predominant (entries 2 and 3). Although no photoreaction of *t*-butyl hydroxamate **14d** occurred at all, to our delight, we found that the irradiation of *t*-butyl amide **14e** afforded the corresponding cyclopropanol **15e** in 71% yield (entries 4 and 5). In addition, the photo-reaction of the trityl-protected amide **14f** proceeded cleanly (entry 6), though with only moderate conversion. Since transient formation of the hemiacetal with methanol may disturb the reaction,[18] solvent screening was performed (see Table S1).[17] We found that the use of 2-butanol was effective, providing **14f** in almost quantitative yields (entry 7). Furthermore, it was found that the photo-reaction of the simple (*N*-non-substituted) 3,3-dimethyl-2-oxobutyramide (**14g**) was completed within 5 min, and 1-hydroxy-2,2-dimethylcyclopropanecarboxamide (**15g**) was obtained in 94% yield (entry 8).

With this knowledge of the effects of N-atom substituents and solvent in hand, we next investigated variations of the ketone. For easy monitoring of the proto-reaction by TLC, UV-active trityl-protected amides **16** were selected (Scheme 2). Preparation of **16** is shown in Schemes S3–S5.[17] Photo-reaction of **16a**–**16c** bearing a substituent Y (Me, OBn, or OTBS) proceeded smoothly to provide the corresponding cyclopropanols *syn*-**17a**–**17c** and their diastereomers *anti*-**17a**–**17c** in excellent yields. The stereochemistry of these products was mainly determined from their HMBC spectra. Namely, a stronger HMBC correlation from H^a to the C-atom of the amide carbonyl group was observed in the major isomers. We considered that this would be attributed to the *syn*-orientation (dihedral angle = ~0°) of these atoms, which should show a larger coupling constant (*J* value) than the corresponding *anti*-isomers (dihedral angle = ~135°). This consideration was supported by DFT calculations as well as by the different intensities of the HMBC correlations observed between H^a and the two methyl groups on cyclopropanols (Figs. S2–S6).[17]

It should be noted that no cyclized product at the methyl group **18a**–**18c** was detected in the photochemical reaction of **16a**–**16c**. In contrast, the reaction of **16d** with an acetoxy group provided regio-isomer **18d** as a major product (80%) along with a small amount of *syn*-**17d** (4%). The stereochemistry of these molecules was assigned in the same manner as described above (see also Figs. S7–S8).[17] These results indicated that the selective formation of cyclopropanols **17** and **18** can be achieved by the choice of a suitable substituent on the O-atom. On the other hand, photolysis of non-protected **16e** did not produce any cyclopropanol derivative. Instead, disproportionation occurred to give **19** in moderate yields.[19] In addition, **16f** with a bromine atom was converted to



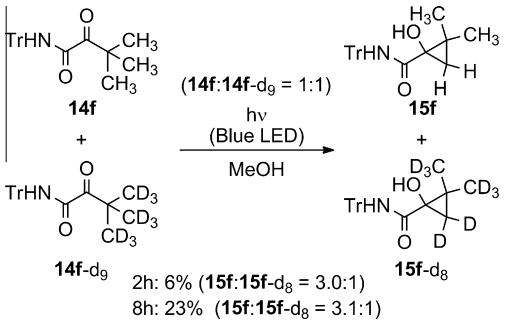
Scheme 2. Photo-induced cyclopropanol formations of α-ketoamides **15**.

β,γ-unsaturated α-ketoamide **20** through cyclopropanol formation followed by simultaneous β-elimination and ring-opening.

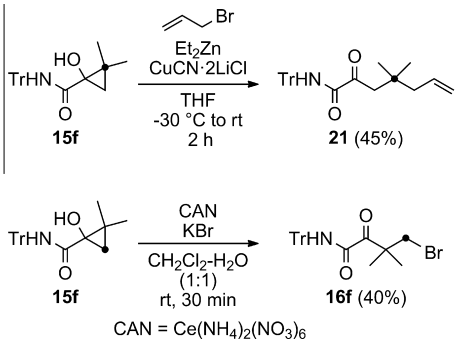
This reaction was applicable to substrates with bulkier substituents, and photolysis of **16g** and **16h** afforded the unique cyclopropanols **17g**, **17h**, and **18h**. In all cases, H-atoms on the more-substituted carbon center were selectively abstracted, as in the reactions of **16a**–**16c**. On the other hand, photo-reaction of the sterically less demanding isopropyl or ethyl α-ketoamide gave messy mixtures, suggesting that close proximity between the amide functionality and the reaction site is significant for this transformation.

Chesta and Whitten reported that little kinetic isotope effect (KIE) was observed in the reaction of *N*,*N*-disubstituted α-ketoamides **1** to give β-lactam derivatives **2** and/or oxazolidinone **3**, even when the Nα-proton of the substrate **1** was replaced with deuterium.[8] These results indicated that H-atom abstraction is not the rate-determining step in the photo-chemical reaction of **1**. On the other hand, significant KIE was observed in our reaction. Photolysis of the mixture of **14f** and **14f**-d_9 (1:1) gave a mixture of **15f** and **15f**-d_8 (2 h: yield 6%, KIE = 3.0; 8 h: yield 23%, KIE = 3.1), clearly indicating that H-atom abstraction is involved in the rate-determining step of the cyclopropanol formation reaction (Scheme 3).

Finally, the ring-opening reaction of cyclopropanol **15f** was examined (Scheme 4). Treatment of **15f** with allyl bromide in the presence of Et_2Zn and CuCl·2LiCl gave ring-opening product **21** with the allyl group at the more-substituted carbon in a site-selective manner in moderate yields. It should be noted that this was an unexpected result, since this condition was reported to open the cyclopropanol ring and lead to the introduction of an allyl unit via S_N2' reaction at the less-hindered carbon center.[20] The amide group might contribute to the change of site-selectivity



Scheme 3. Photolysis of the mixture of **14f** and **14f**-d_9.



Scheme 4. Allylation and bromination of cyclopropanol **15f**.

of ring-opening. After several investigations, we found that the treatment of **15f** with $Ce(NH_4)_2(NO_3)_6$ (CAN) and KBr[21] resulted in the introduction of bromine at the less-hindered site of cyclopropanol to produce **16f** in moderate yields. These results suggest that a variety of α-ketoamide derivatives could be prepared from the photo-products by selecting the appropriate ring-opening method.

In conclusion, we have developed novel blue LED-induced cyclopropanol formation reaction from α-ketoamides. This process has the potential for the synthesis of highly substituted cyclopropanol derivatives bearing amide functionality. The corresponding diradical-like precursor **11** appears to be generated by H-atom abstraction by the amide group, which is the rate-determining step, in contrast to the known Norrish-type II process of α-ketoamides. Further investigations are in progress.

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Supplementary data

Supplementary data (additional figures and a table (Figs. S1–S8, Schemes S1–S5, and Table S1), preparation of substrate α-ketoamides, characterization data for new compounds, representative experimental procedures, and ^1H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.038.

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